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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/928,191	08/11/2001	Christophe Schilling	UCSD 99-093	6758
28213	7590	02/26/2008		
DLA PIPER US LLP 4365 EXECUTIVE DRIVE SUITE 1100 SAN DIEGO, CA 92121-2133			EXAMINER CLOW, LORI A	
			ART UNIT	PAPER NUMBER
			1631	
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

**Application No.**

09/928,191

**Applicant(s)**

SCHILLING, CHRISTOPHE

**Examiner**

Lori A. Clow, Ph.D.

**Art Unit**

1631

**-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 November 2007.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-8, 10, 12 and 14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 1-8 is/are allowed.
- 6) ☒ Claim(s) 10, 12, 14 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB/C)
- Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 21 November 2007 has been entered.

Claims 1-8, 10, 12, and 14 are currently pending. Claims 12 and 14 are hereby rejoined, as claim 1-8 have been deemed allowable. Claims 9, 11, 13, and 15-27 have been cancelled.

#### **Claim Rejections - 35 USC § 112-1st paragraph**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 12 and 14 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or

absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must be able to analyze the production of one or more selected metabolites of a biochemical reaction network producing metabolites in which the reaction network **is an organism** producing desired bio-molecules or **is an organism** producing desired bio-molecules by multiple metabolic routes. For the reasons set forth below, this represent undue experimentation.

b) The specification provides that the biochemical reaction network represent a disease, as in the following passage cited for example:

As another example, the biochemical reaction network that is analyzed can again **represent a disease-producing, pathogenic, organism**. However, this time the metabolite of interest can be the actual disease-producing, deleterious, substance that is produced by the pathogenic organism. In this situation the method of the present invention using the reaction set can be directed to targeting the development of a drug that, by obstructing those reactions of the pathogenic organism that produce the metabolite that induces disease, serves to eliminate the deleterious, disease-causing, function of the pathogenic organism (page 11, lines 21-30).

The specification cites that the method of the present invention consists of using convex hull to represent the capabilities of a metabolic genotype, for example (page 13, line 16-18) or to represent a metabolic phenotype (page 13, line 27-30). The reactions determined are representative of the physical –chemical conversions that occur within a system (page 20, lines 3-5). The mathematical description of reactions in a cellular network by the addition and removal of constraints on internal and exchange fluxes simulates genetic deletion events, complete enzymatic inhibition or stimulation of metabolic resources in a network (page 26, lines

4-10). Thus, the specification describes biochemical reaction network that only **represent** disease or otherwise **represent** an organism. The specification, however, does not provide for a reaction network that actually **IS** an organism, as is claimed in claims 12 and 14.

c) The specification contains one example of minimal deletion sets in a hypothetical reaction network in which deletion sets are calculated. The network has 6 metabolites, 8 internal fluxes and 5 exchange fluxes. Reactions of the network are determined and mass balance equations are assembled to generate a stoichiometric matrix. Extreme pathways are then determined and area calculated. Linear optimization techniques may also be used to analyze single and double deletion combinations within a network (pages 27-30; Example 1).

Therefore, the example set forth in the specification teaches a reaction network with metabolic inputs. However, the example does not provide for a reaction network that **IS** an organism. Therefore, the specification does not enable the claim to a “reaction network analyzed that **IS** an organism producing desired bio-molecules”.

d) The invention is drawn to methods of analyzing the production of one or more selected metabolites of a biochemical reaction network in which the reaction network is an organism. However, the instant specification does not enable such claims, as it only enables the analysis of a reaction network the represents an organism, as stated above.

e) and g) It would have been well known in the art that flux balance analysis can be performed to analyze metabolic system (see Schilling (Biotech. Bioeng. (2001) pages 286-306; previously cited). Schilling teaches the analysis of systemic properties of cellular metabolism through mathematical modeling of a network that represents an organism, but is not an actual organism itself (see abstract).

f) The skill of those in the art of bioinformatics is high.

h) The claims are not enabled because they are drawn to a reaction network that IS an organism. The skilled practitioner would first turn to the instant specification for guidance to practice such methods. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows that reaction networks represent organisms but are not actually organisms themselves. Finally, said practitioner would turn to trial and error experimentation. Such represents undue experimentation

#### **Claim Rejections - 35 USC § 112**

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10, 12 and 14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites, "using the reaction set for targeting the development of a drug that, by obstructing those reactions of the pathogenic organism produce the metabolite that induces disease, serves to eliminate the deleterious, disease-causing, function of the pathogenic organism". It is unclear what is intended by this phrase, as the sentence is incomplete. Perhaps Applicant intends the limitation to be as follows: "using the reaction set for targeting the development of a drug that, by obstructing those reactions of the pathogenic organism **that**

produce the metabolite that induces disease, serves to eliminate the deleterious, disease-causing, function of the pathogenic organism". Clarification is requested.

Claims 12 and 14 recite, "wherein the reaction network analyzed is an organism". It is unclear how a reaction network can physically be an organism. Perhaps it is intended that the reaction network represent an organism. Clarification is requested.

Claim 12 recites, "wherein the reaction network analyzed is an organism producing desired bio-molecules of value and undesired bio-molecules of both no value". It is unclear what is intended by this limitation. Perhaps Applicant intends that the claim read, "wherein the reaction network analyzed represents an organism producing desired bio-molecules of value and undesired bio-molecules of no value". Clarification is requested.

Claim 12 recites, "wherein the metabolite of interest produced by the of the undesired valueless bio-molecules". It is unclear what is intended by this limitation. Perhaps Applicant intends the claim to read, "wherein the metabolite of interest produced by the organism is the undesired valueless bio-molecule". Clarification is requested.

Claim 12 recites, "using the reaction set to metabolically re-engineer the organism to fail of those reactions that produce the metabolite of that is undesired and valueless, therein eliminating production of undesired valueless bio-molecules while permitting production of organism is desired valued bio-molecules". It is unclear what is intended by this limitation. It is nonsensical. Clarification is requested.

Claim 14 recites, "using the reaction set to metabolically re-engineer the organism to fail of those reactions that produce the metabolite of interest via the one route therein by eliminating production of metabolite via this route, nonetheless that the metabolite is of value, leaving intact

production of the same metabolite by alternative ones of the multiple metabolic routes". It is unclear what is intended by this limitation, as it is nonsensical grammatically. Clarification is requested.

### **Conclusion**

Claims 1-8 are allowed, as stated in the Advisory Action of 23 August 2007. The prior art does not teach or fairly suggest the method of analyzing the production of one or more selected metabolites of a biochemical reaction network producing metabolites using linear equations and inequalities of the network mathematically forming a convex solution space (flux cone), calculating vectors of the flux cone and generating extreme pathways.

Claims 10, 12, and 14 are rejected, as stated above.

### **Inquiries**

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The Central Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marjorie Moran can be reached on (571) 272-0720.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Art Unit: 1631

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/Lori A. Clow, Ph.D./

Primary Examiner, Art Unit 1631

February 28, 2008

**Application Number****Application/Control No.**

09/928,191

**Applicant(s)/Patent under  
Reexamination**

SCHILLING, CHRISTOPHE

**Examiner**

Lori A. Clow, Ph.D.

**Art Unit**

1631